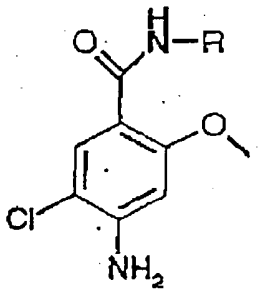
CLAIMS

1. Use of one or more compounds having agonist activity to a 5-$HT_4$ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising the following 5-$HT_4$ receptor agonists: benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopramide, with the structural formula:

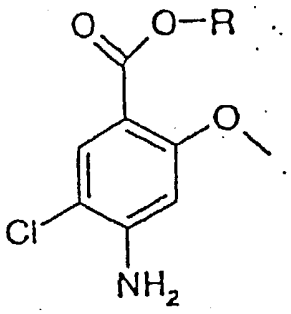



having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

**AMENDED SHEET**

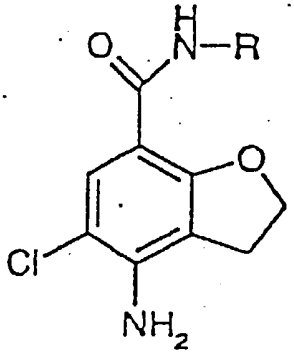
**AMENDED SHEET**

benzoic acid esters:

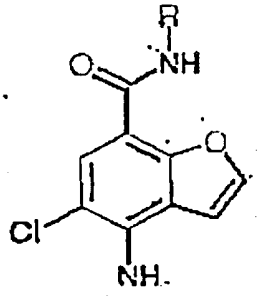


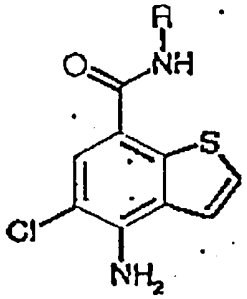
preferably ML 10302, RS 57639, and SR 59768;

a 2,3-dihydro-bensofuran-7-carboxamide compound, preferably ADR 932, Prucalopride (=R 093877), and SK-951;

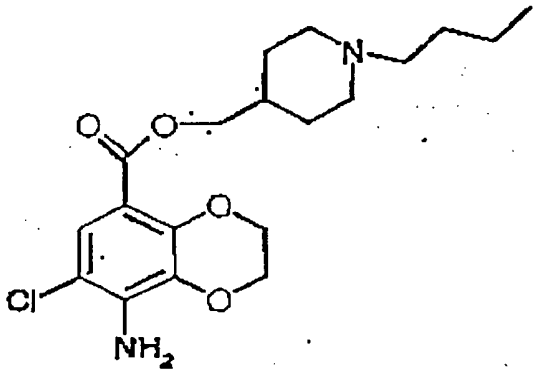


benzofuranes and benzotiophenes,



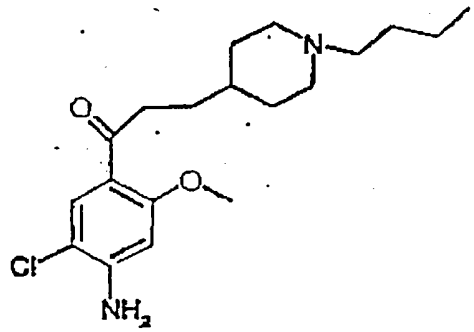


the benzodioxan



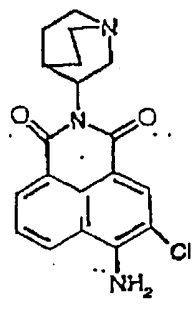
SB 204070

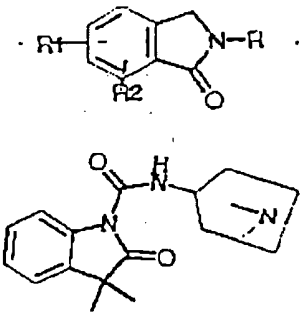
the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone



e.g. preferably RS 67333 and RS 17017;

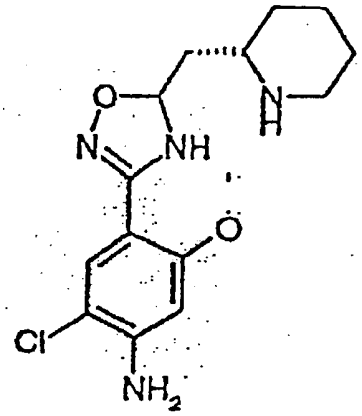
naphtalimides, preferably RS 56532;





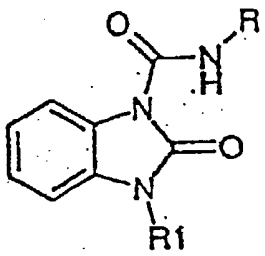
benzindolones;

compounds in which the amide function has been replaced with an oxadiazol ring;



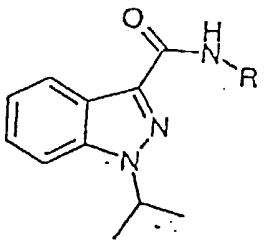
preferably YM-53389;

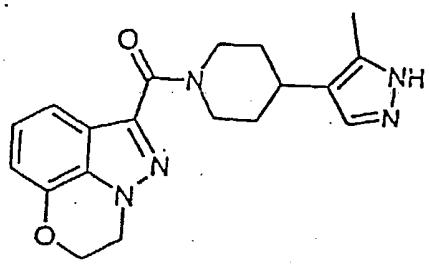
benzimidazolone-1-carboxamides



preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

the carboamides

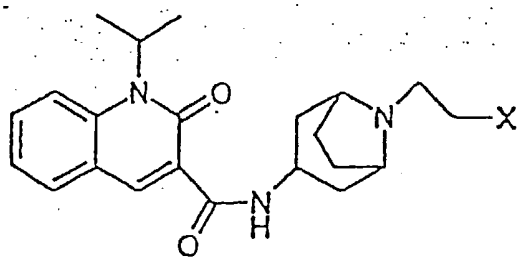




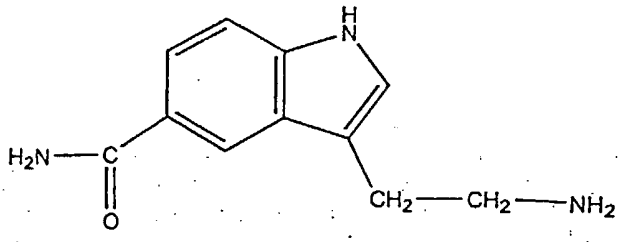
indols, preferably 5-methoxytryptamine, 2-methyl-serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side chain:

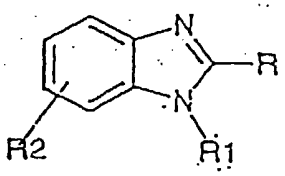
benzokinolinones



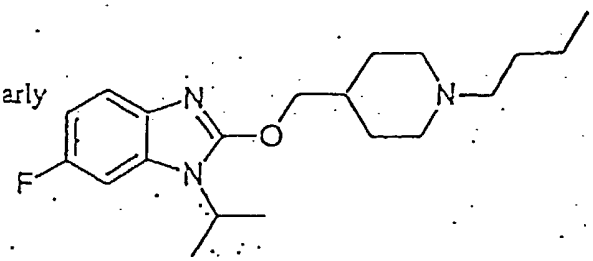
5-carboxamidotryptamine (5-CT), with the structural formula:



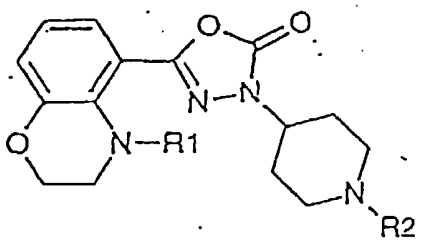
3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,



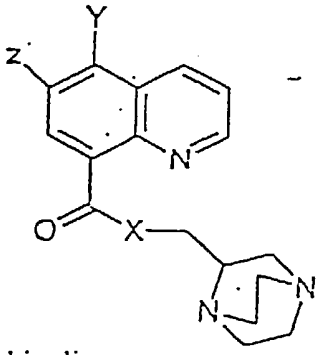
, particularly



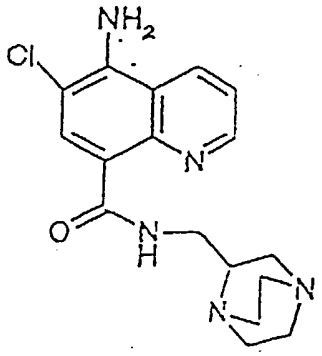
2-piperidinmethylethers of bensimidazol



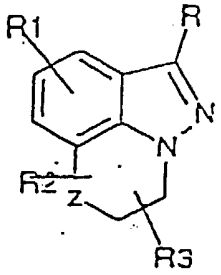
oxadiazalon based substance



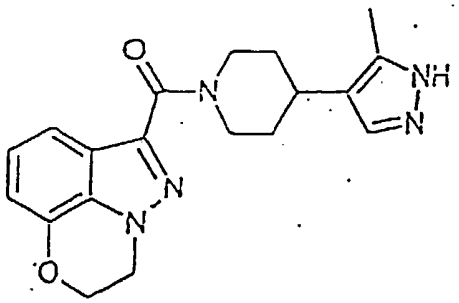
, particularly

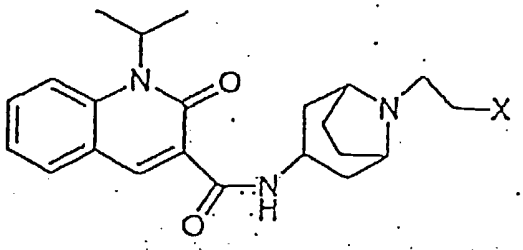


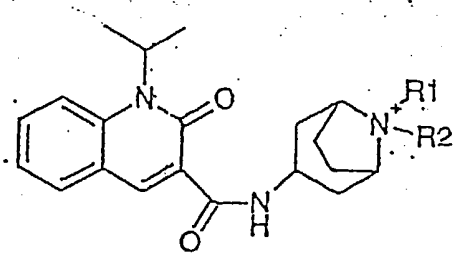
kinolines



, particularly







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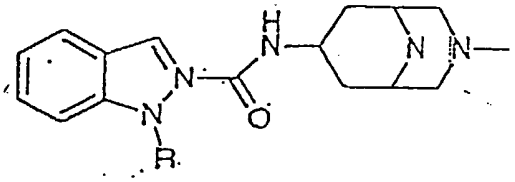
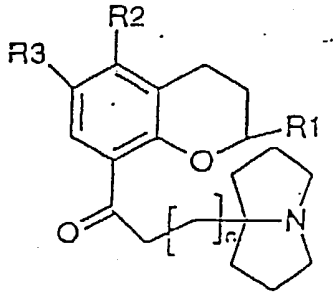
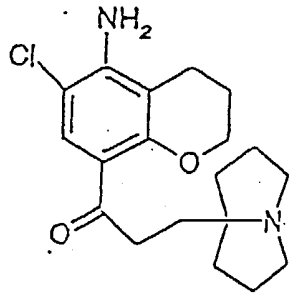
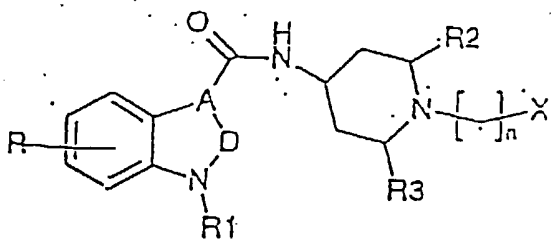


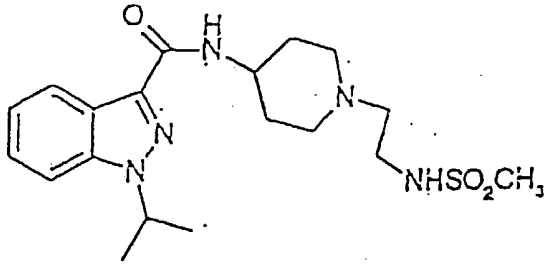


, particularly



benzopyranes





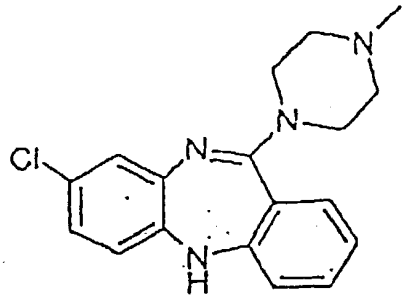
and derivatives and pharmaceutically acceptable salts thereof.

2. Use according to claim 1, wherein said compound is VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine, Zacopride, RS56532, Mosapride, BRL 24924, or SC 53116.

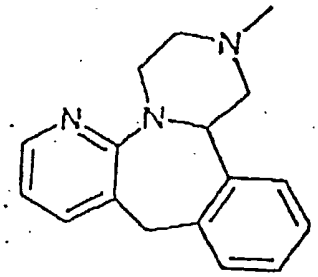
3. Use according to any one of the previous claims, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

4. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according to any one of claims 1 and 2.

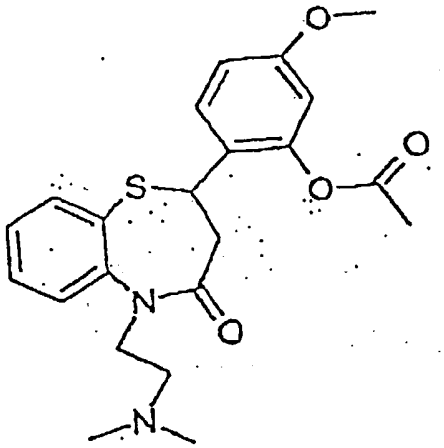
5. Use of one or more compounds having antagonist activity to a 5-$HT_3$ receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-$HT_3$ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 5-$HT_3$ receptor antagonists



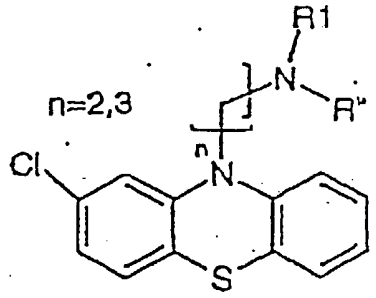
benzazepines, preferably mirtazapine



benztiazephines, preferably diltiazem

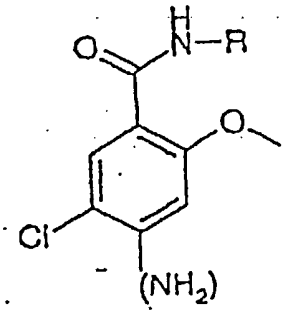


and fentiazines



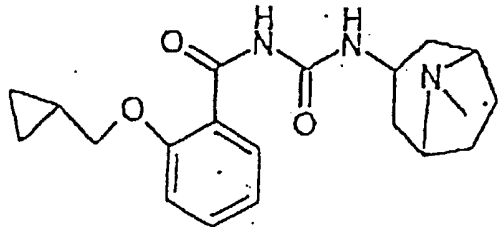

preferably perphenazine, stemetil;

compounds also having 5-$HT_4$ receptor agonist activity, preferably benzamides



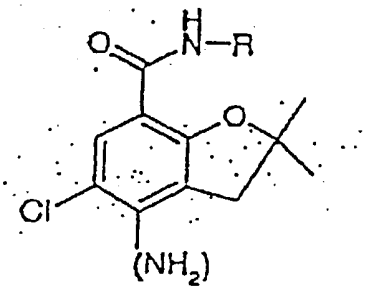
(cisapride, zacopride, mosapride, pancropride, BRL 24924, BMY 33462)

and



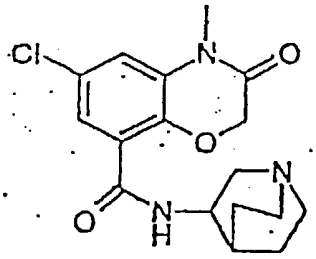
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



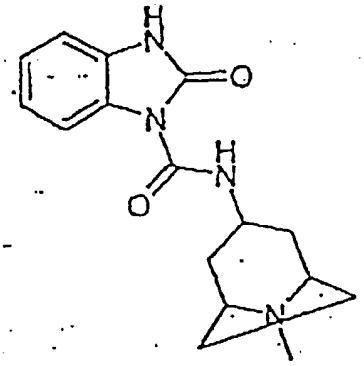
(preferably zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides



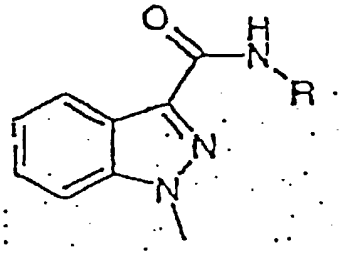
preferably azasetron (=Y25130);

benzimidazolones



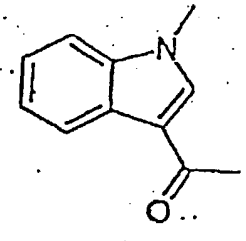
preferably itasetron (=DAU 6215);

indazol-3-carboxamides

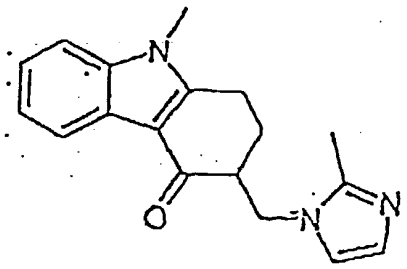


preferably N 3389, LY 278584, DAT 582;

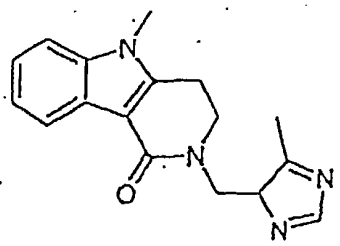
wherein the latter group reminds most of the specific 5-$HT_3$ antagonists, which contains the group



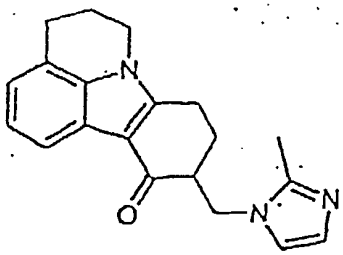
in different forms, such as



ondansetron

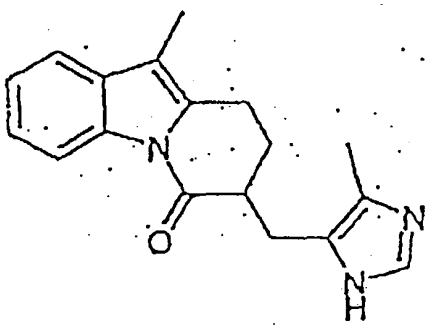


alosetron



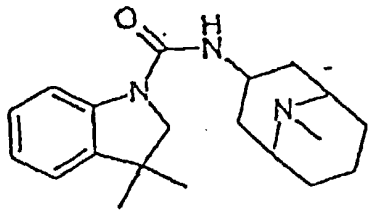
cilansetron

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen



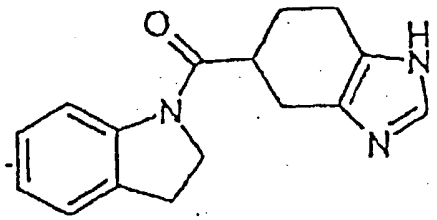
FK 1052

also being an antagonist against both 5-$HT_3$ and 5-$HT_4$ receptors,



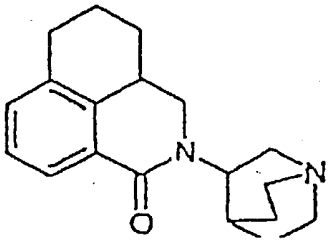
BRL 46470 A

bisindoles

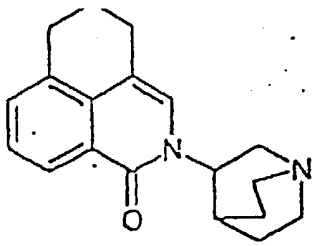


YM 114

isoquinoline-1-ones

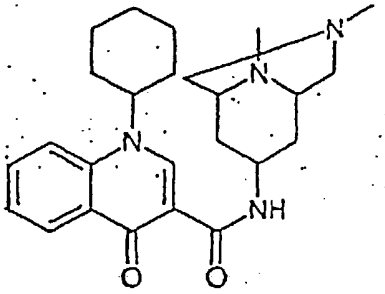


palonosetron (=RS 25259-197)

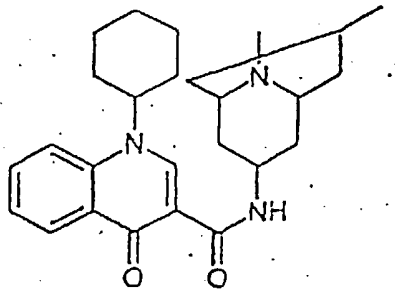


RS 42358-197

and the quinoline-3-carboxamides

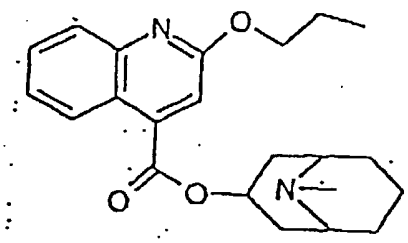


WAY-SEC 579

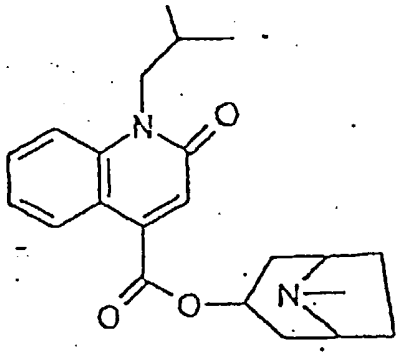


Mirisetron (=WAY 100579),

quinoline-4-carboxylates

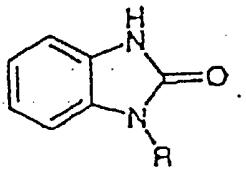


preferably KF 17643



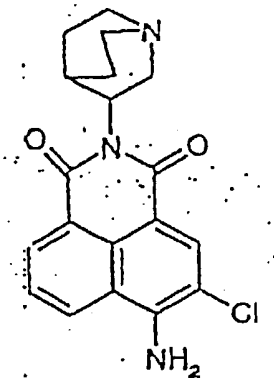
preferably KF 18259;

benzimidazolones



preferably itasetron (DAU6215),

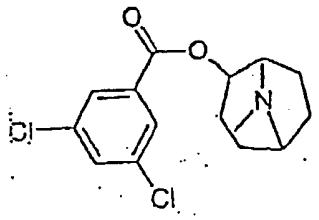
and the naphtimides



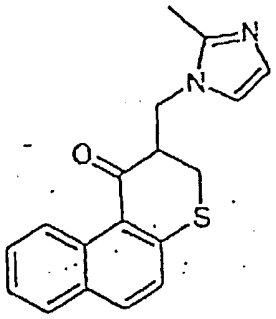
RS 56532

preferably RS 56532;

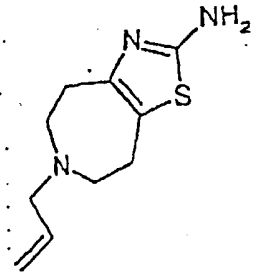
MDL 72222, which also is a specific 5-$HT_3$ antagonist;



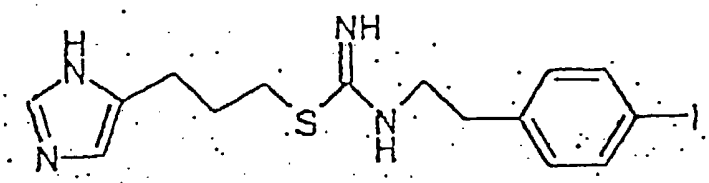
; and



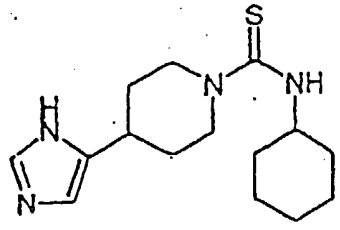
GK 128



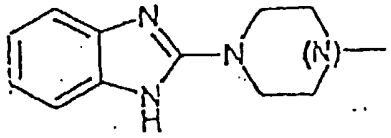
Talipexole



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKI-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide, Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect,

and derivatives and pharmaceutically acceptable salts thereof.

6. Use according to claim 5, wherein said compound is Tropanyl 3,5-dimethylbenzoate, MDL 72222, SDZ 216-525, ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron, or Cilansetron.

7. Use according to any one of claims 5 and 6, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

8. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according to any one of claims 5 and 6.

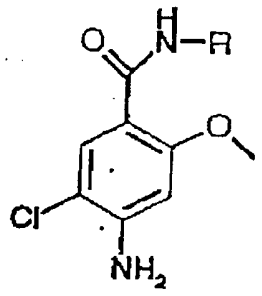
9. Use of a composition comprising a combination of at least one compound with agonist activity to the 5-$HT_4$ receptor, and at least one compound with antagonist activity to the 5-$HT_3$ receptor, for the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, preferably asthma and disorders related thereto.

10. Use according to claim 9, wherein said composition has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said combination is chosen from the following groups of

a) 5-$HT_4$ receptor agonists:

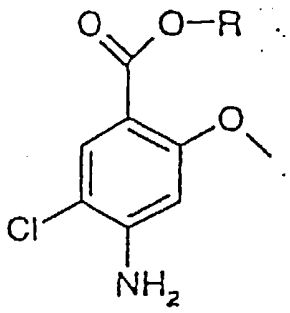
benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopra

mide, with the structural formula:



having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

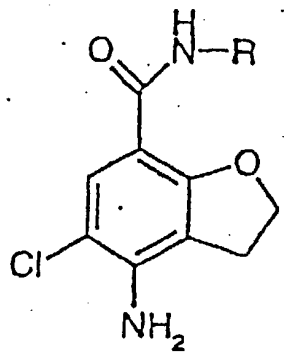
benzoic acid esters:



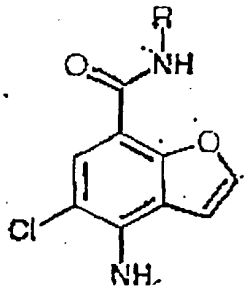
preferably ML 10302, RS 57639, and SR 59768;

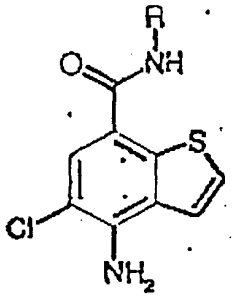
a 2,3-dihydro-bensofuran-7-carboxamide compound,

preferably ADR 932, Prucalopride (=R 093877), and SK-951;

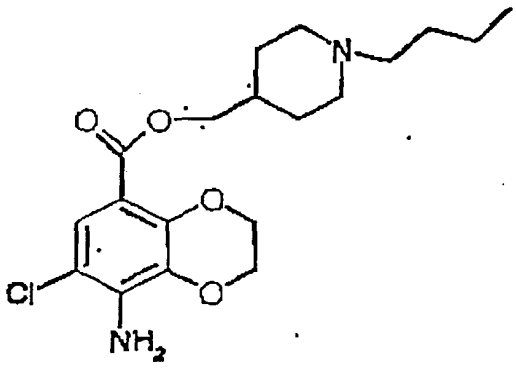


benzofuranes and benzotiophenes,



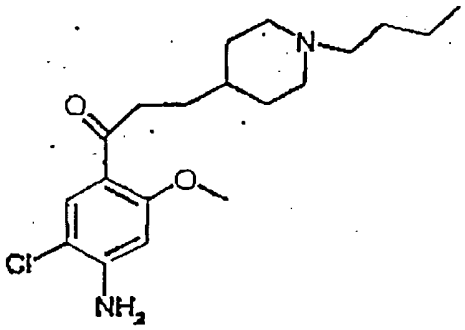


the benzodioxan



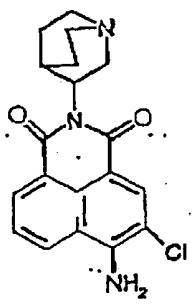
SB 204070

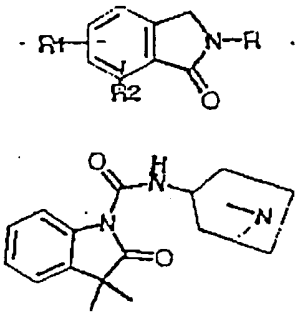
the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone



e.g. preferably RS 67333 and RS 17017;

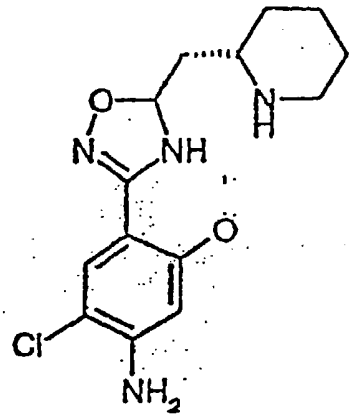
naphtalimides, preferably RS 56532;





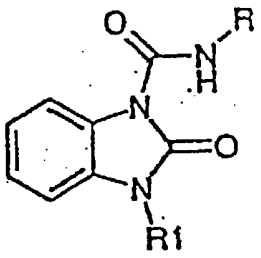
benzindolones;

compounds in which the amide fuction has been replaced with an oxadiazol ring;



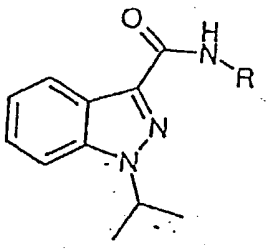
preferably YM-53389;

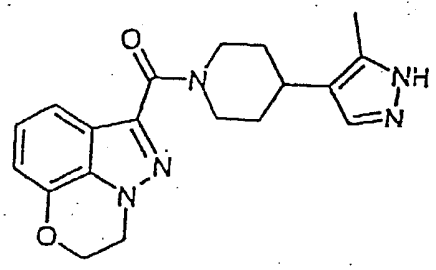
benzimidazolone-1-carboxamides



preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

the carboamides

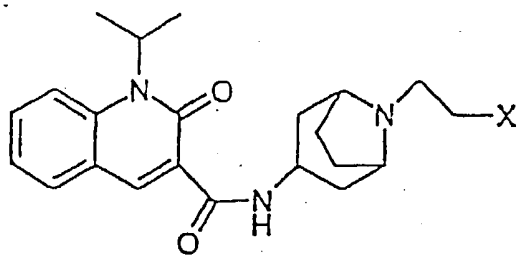




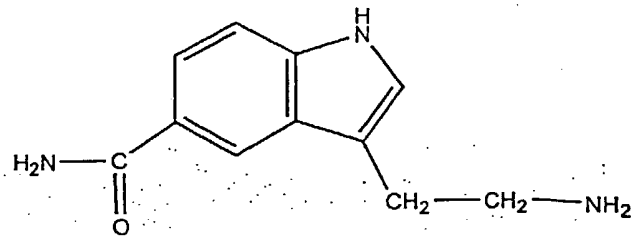
indols, preferably 5-methoxytryptamine, 2-methyl-serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side chain:

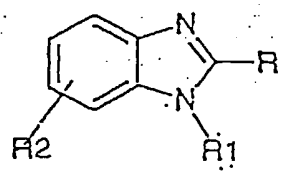
benzokinolinones



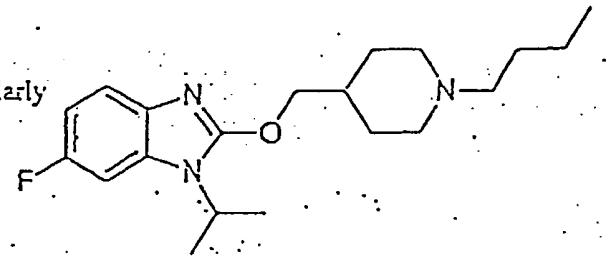
5-carboxamidotryptamine (5-CT), with the structural formula:



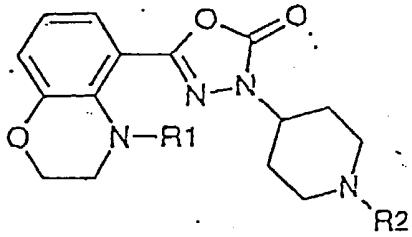
3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,



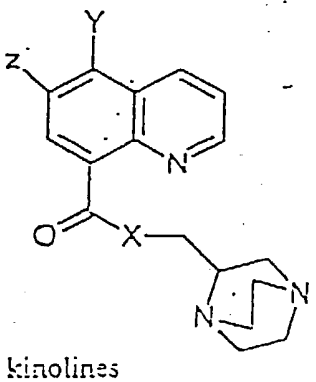
, particularly



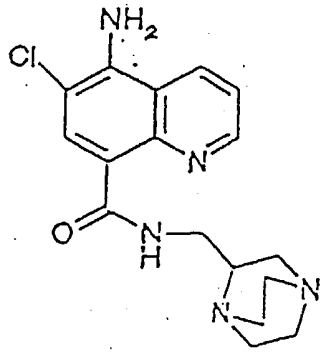
2-piperidinmethylethers of bensimidazol



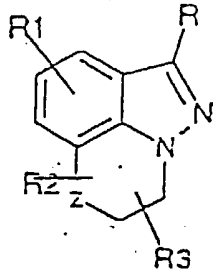
oxadiazalon based substance



, particularly



kinolines



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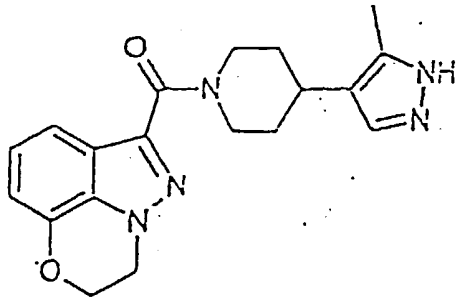
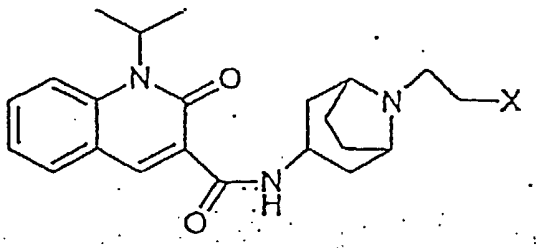
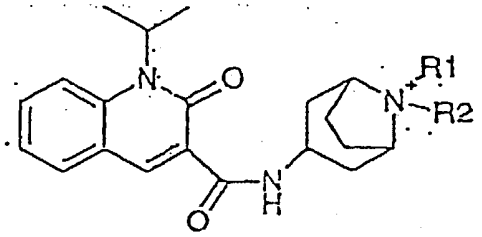
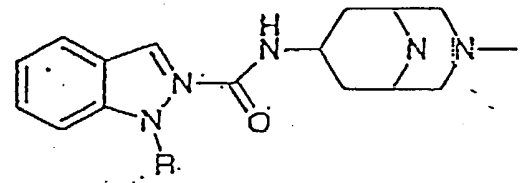
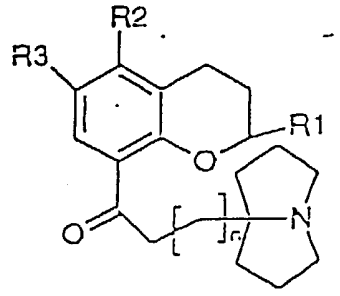






Q





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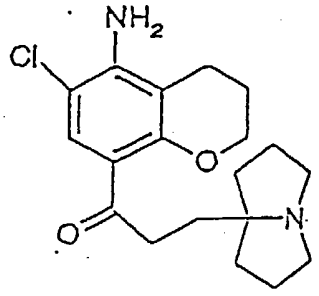
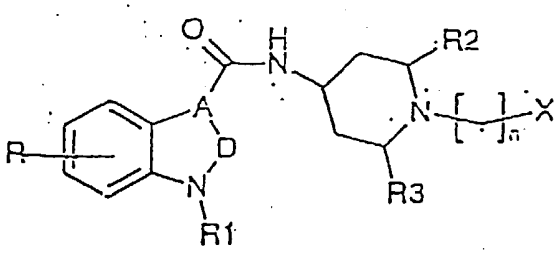
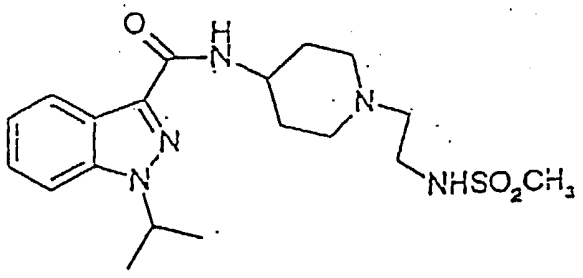


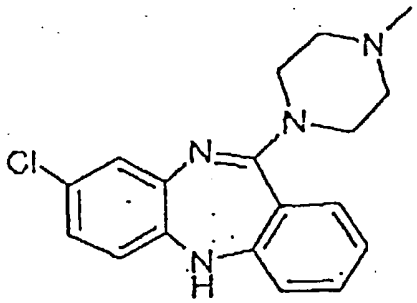
bensopyranes



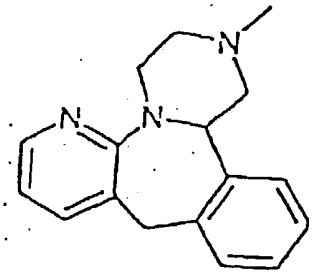


and serotonin (5-HT) and derivatives and pharmaceutically acceptable salts thereof.

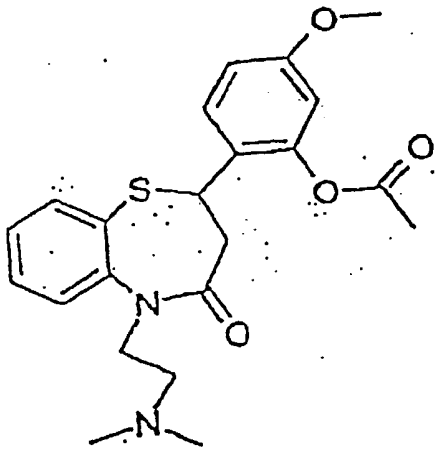
b) $5\text{-HT}_3$ receptor antagonists:



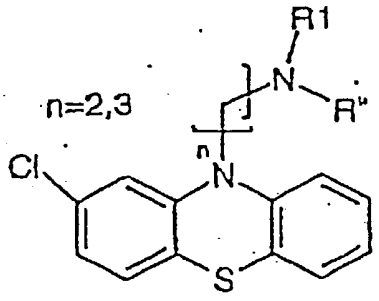
benzazepines, preferably mirtazapine



benztiazephines, preferably diltiazem

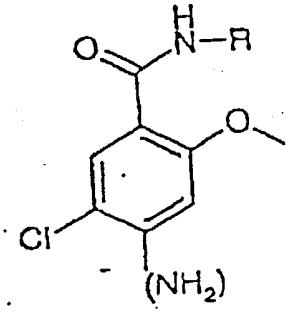


and fentiazines



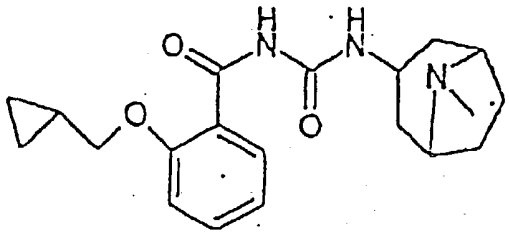

preferably perphenazine, stemetil;

compounds also having 5-$HT_4$ receptor agonist activity, preferably benzamides



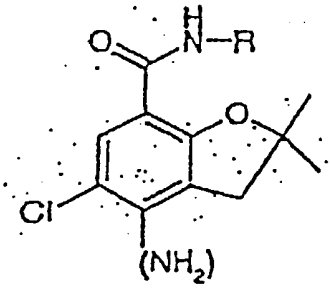

(cisapride, zacopride, mosapride, pancropride, BRL 24924, BMY 33462)

and



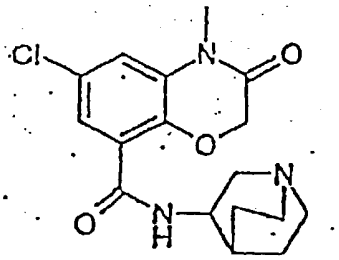

WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



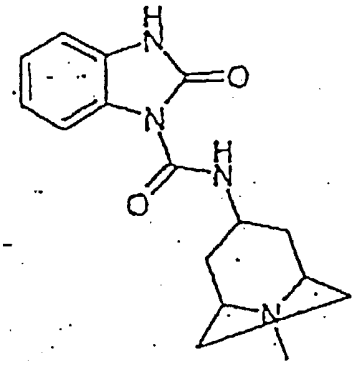
(preferably zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides



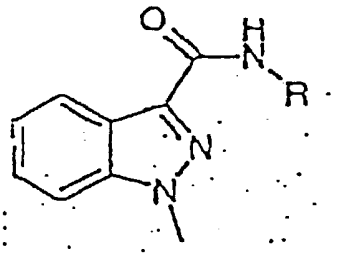
preferably azasetron (=Y25130);

benzimidazolones



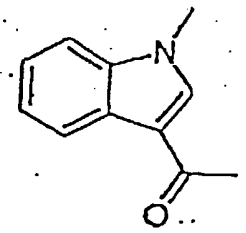
preferably itasetron (=DAU 6215);

indazol-3-carboxamides

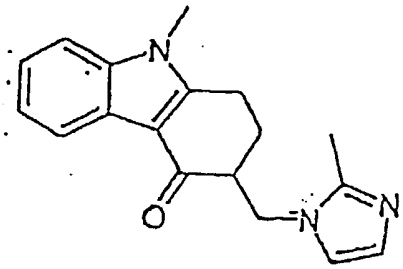


preferably N 3389, LY 278584, DAT 582;

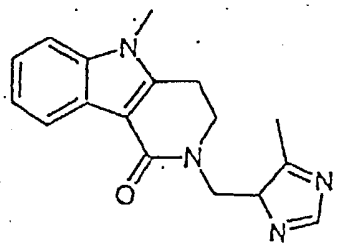
wherein the latter group reminds most of the specific 5-$HT_3$ antagonists, which contains the group



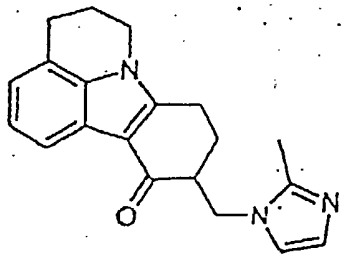
in different forms, such as



ondansetron

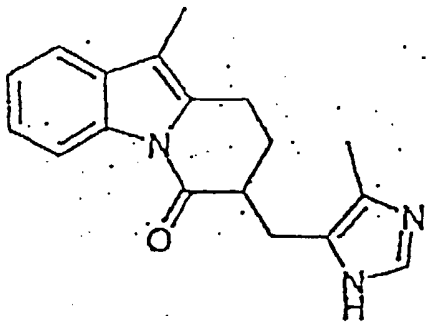


alosetron



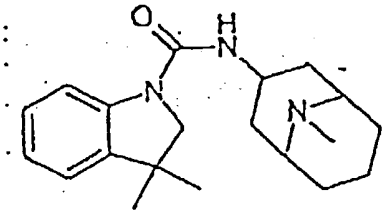
cilansetron

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen



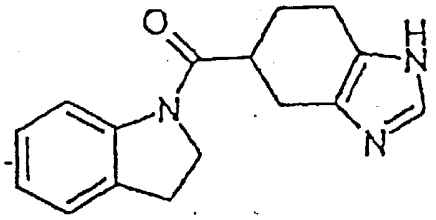
FK 1052

also being an antagonist against both 5-$HT_3$ and 5-$HT_4$ receptors,



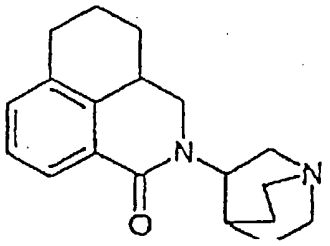
BRL 46470 A

bisindoles

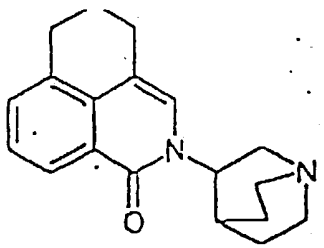


YM 114

isoquinoline-1-ones

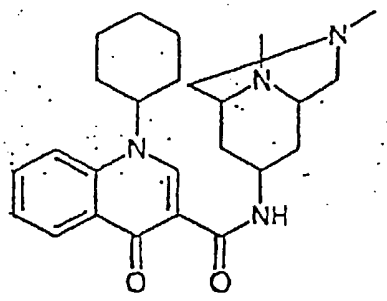


palonosetron (=RS 25259-197)

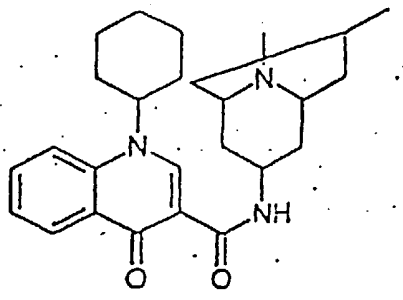


RS 42358-197

and the quinoline-3-carboxamides

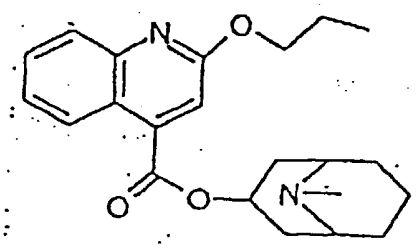


WAY-SEC 579

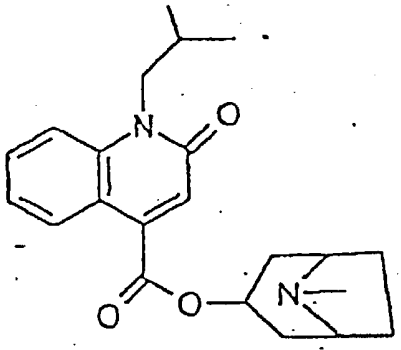


Mirisetron (=WAY 100579),

quinoline-4-carboxylates

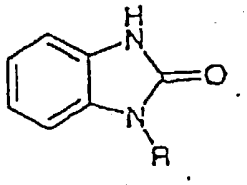


preferably KF 17643



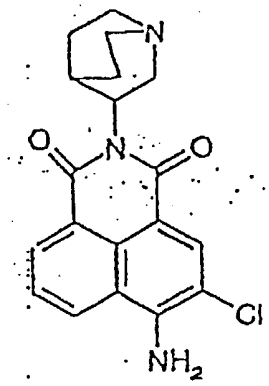
preferably KF 18259;

benzimidazolones



preferably itasetron (DAU6215),

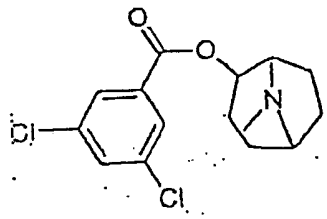
and the naphtimides



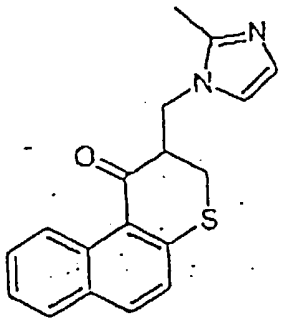
RS 56532

preferably RS 56532;

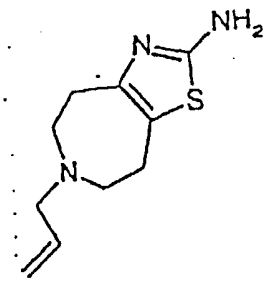
MDL 72222, which also is a specific 5-$HT_3$ antagonist;



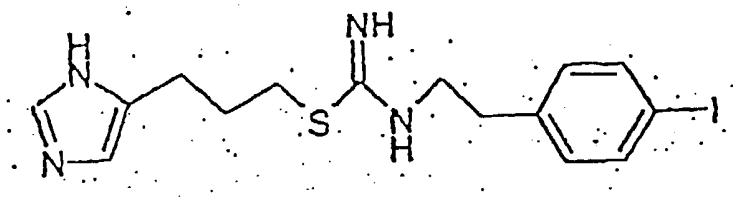
; and



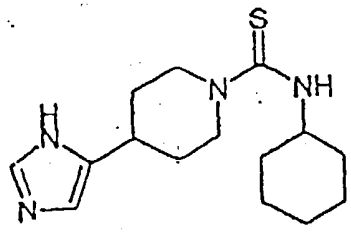
GK 128



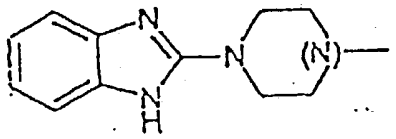
Talipexole



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide,

Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect, and derivatives and pharmaceutically acceptable salts thereof.

11. Use according to claim 10, wherein the composition comprises the following combinations of a 5-$HT_4$ receptor agonist and a 5-$HT_3$ receptor antagonist: VB20B7 and Tropanyl 3,5-dimethylbenzoate, VB20B7 and MDL 72222, RS67333 and Tropanyl 3,5-dimethylbenzoate, RS76333 and MDL 72222, VB20B7 and ICI 169369, RS67333 and ICI 169369, Zacopride and Tropanyl 3,5-dimethylbenzoate, Zacopride and MDL 72222, RS56532 and Tropanyl 3,5 dimethylbenzoate, RS56532 and MDL 72222, Itasetron and Tropanyl 3,5-dimethylbenzoate, Itasetron and MDL 72222, VB20B7 and SDZ 216-525, and RS67333 and SDZ 216-525.

12. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a composition according to any one of claims 10 and 11.

13. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease,

wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a 5-$HT_4$ receptor agonist according to any one of claims 1 and 2 and a 5-$HT_3$ receptor antagonist according to any one of claims 5 and 6, either simultaneously or sequentially.